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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/522,150	01/24/2005	Dan Peters	2815-0297PUS1	9211
2292 7590 11/13/2007 BIRCH STEWART KOLASCH & BIRCH PO BOX 747 FALLS CHURCH, VA 22040-0747			EXAMINER O DELL, DAVID K	
			ART UNIT 1625	PAPER NUMBER
			NOTIFICATION DATE 11/13/2007	DELIVERY MODE ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mailroom@bskb.com

Office Action Summary	Application No. 10/522,150	Applicant(s) PETERS ET AL.	
	Examiner David K. O'Dell	Art Unit 1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 29 October 2007.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 37-65 is/are pending in the application.
4a) Of the above claim(s) 41-43, 47-55 and 57-65 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 37-40, 44-46 and 56 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☒ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date <u>See Continuation Sheet</u> . | 6) <input type="checkbox"/> Other: _____ |

Continuation of Attachment(s) 3. Information Disclosure Statement(s) (PTO/SB/08), Paper No(s)/Mail Date :24 January 2005 & 22 April 2005.

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DETAILED ACTION

1. This application is a 371 of PCT/DK03/00538 filed 08/13/2003 which claims priority to Danish application PA 2002-01208 filed 08/14/2002 and Danish application 2002 01472 filed 10/02/2002.
2. Claims 37-65 are pending.

Response to Restriction/Election

3. Applicant's election of group III and the species (\pm)-3-[6-Thienyl)-pyridazin-3-yloxy]-1-aza-bicyclo[2.2.2]octane, without traverse in the reply filed on October 29, 2007 is acknowledged. This requirement is made FINAL. This application contains claims drawn to a nonelected invention. A complete reply to this action must include a cancellation of nonelected claims or other appropriate action.

Under examination:

Group III, Claims 37-40, 44, 45, 46, 56 drawn to compounds and compositions reading on n is 2, X is O, A is pyridazine drawn to azabicycl[2.2.2]octane-pyridazine-ethers.

Claim Rejections – 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

4. Claims 37-40, 44-46, 56 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mitch et. al. WO97/20819 OR Merritt et. al. WO96/12711 OR Husbands U. S. Patent 5,512,574 OR Boddick et. al. 5,888,999 AND Chokai et. al. EP 555, 478, in view of U.S. 5,948,793. The

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factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

The claims are drawn to compounds of Formula I, claim 1, where X is O, and A is pyridazine, where the pyridazine is variously substituted.

Determination of the scope and content of the prior art

(MPEP 2141.01)

Mitch et. al. teaches compounds that are analogs of the compounds of the instant case that have the same utility. In particular the compounds on page 48-49:

azabicyclo[2.2.2]octyloxy)]-pyrazine, 3-methoxy-4-(1-
, and others with various substituents.

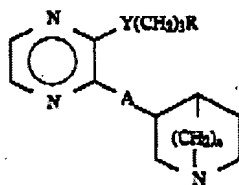
Merritt et. al. teaches compounds that are analogs of the compounds of the instant case that have the same utility. In particular the compounds on page 58-59:

(\pm)-3-Chloro-2-(1-azabicyclo[2.2.2]octyl-3-oxy)pyrazine

, and others with various substituents.

Husbands also teaches a genus of pyrazinyloxy-quinuclidines with various substituents (column 1, where A is O and n is 2)

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in which Y is oxygen or sulfur;

A is oxygen, sulfur or --NR_2 , where R_2 is hydrogen or alkyl of 1 to 6 carbon atoms;

R is $\text{--CH}_2\text{CH}_3$, $\text{--CH}_2\text{CH}_2\text{CH}_3$, $\text{--CH}(\text{CH}_3)_2$,
 $\text{--CH}_2\text{CH}(\text{CH}_3)_2$, $\text{--CH}_2\text{CF}_3$, $\text{--CH}_2\text{CH}_2\text{CF}_3$,
 $\text{--CH}(\text{CF}_3)_2$, $\text{--CH}_2\text{CH}(\text{CF}_3)_2$, $\text{--C}_3\text{H}_7$, $\text{--CH}_2\text{C}_3\text{H}_7$,
 $\text{--CH}_2\text{CH}_2\text{C}_3\text{H}_7$, $\text{--C}_6\text{H}_5$, $\text{--CH}_2\text{C}_6\text{H}_5$, $\text{--C}_2\text{H}_5$,
 $\text{--CH}_2\text{C}_2\text{H}_5$, $\text{--C}_6\text{H}_{10}$, $\text{--CH}_2\text{C}_6\text{H}_{10}$, $\text{--C}_4\text{H}_9\text{S}$,
 $\text{--CH}_2\text{C}_4\text{H}_9\text{S}$, $\text{--C}_6\text{H}_5$ or $\text{--CH}_2\text{C}_6\text{H}_5$;

and n is one of the integers 1 or 2;

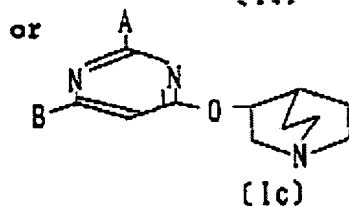
or a pharmaceutically acceptable salt thereof.

Boddick et. al. also teaches these of pyrazinyloxy-quinuclidines with various substituents

(column 13, line 50)

Some examples of compounds contemplated for use in treating anxiety include, but are not limited to: 2-[exo-(+/-)-3-[1-azabicyclo[3.2.1]octyloxy]]pyrazine, 3-butythio-2-(1-azabicyclo[2.2.2]octyl-3-oxy)]pyrazine, 3-butyloxy-2-[3- \pm -endo-(1-azabicyclo[2.2.1]heptyloxy)]pyrazine, 3-(2-butyloxy)-2-[6- \pm -endo-(1-azabicyclo[3.2.1]octyloxy)]pyrazine, 3-hexylthio-2-[6- \pm -exo-(2-azabicyclo[2.2.1]heptyloxy)]pyrazine, 3-(3-phenylpropynylthio)-2-[2- \pm -exo-(7-azabicyclo[2.2.1]heptyloxy)]pyrazine, 3-(2-methylthioethoxy)-2-[3- \pm -exo-(1-azabicyclo[3.2.1]octyloxy)]pyrazine, 3-propargyl-2-[4-(1-azabicyclo[2.2.1]heptyloxy)]pyrazine, and 3-cyclopropylmethylthio-2-[2- \pm -exo-(8-azabicyclo[3.2.1]octyloxy)]pyrazine.

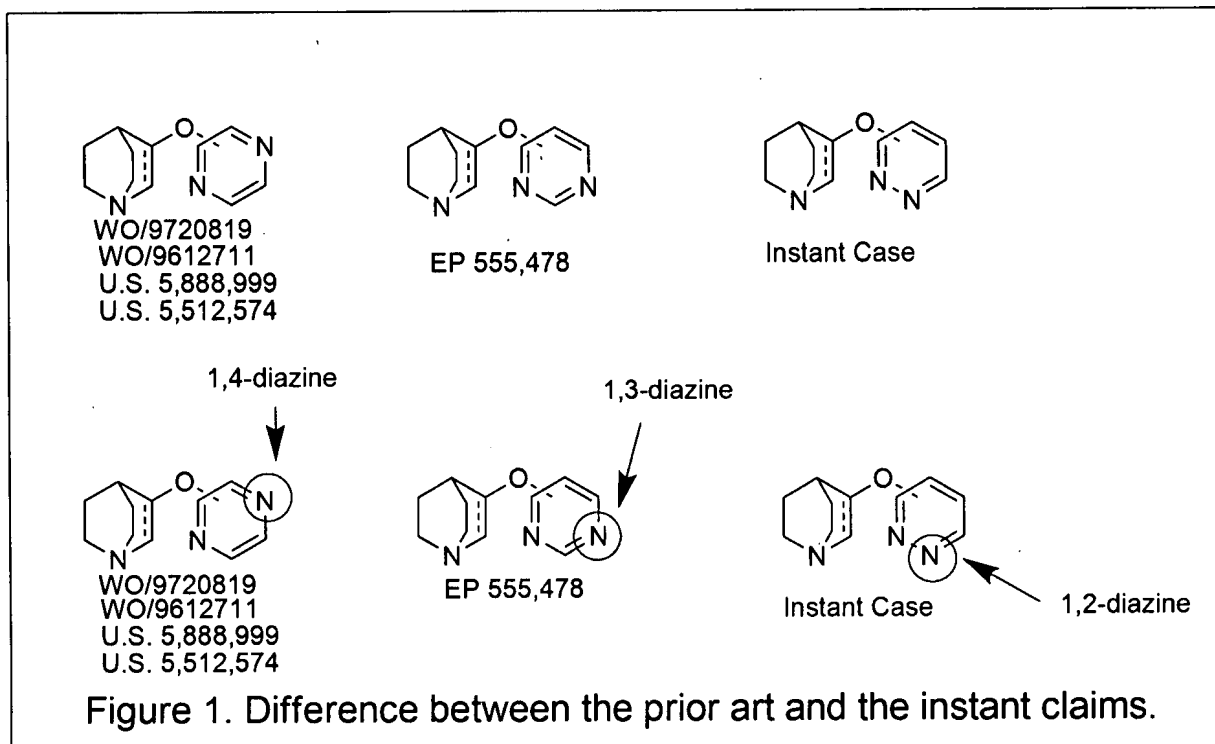
Chokai et. al. teach a large genus of pyrimidinyloxy-quinuclidines bearing various substituents pg. 7



U.S. 5,948,793 teaches that the pyridazine moiety is associated with activity at the nicotinic acid acetylcholine receptor (see example 13).

Ascertainment of the difference between the prior art and the claims

It is clear that the instant claims differ from the prior art only by the position of the nitrogen atom in the six-membered ring. This is represented graphically in Figure 1.



The pyrazines (1,4-diazines) were known and the pyrimidines (1,3-diazines) were known and the instant case is drawn to the obvious missing member, namely the pyridiazines (1,2-diazines).

(MPEP 2141.02)

None of the above inventors teach the exact compounds of the instant case. The difference however is only the position of the nitrogen atom in the six-membered ring.

Finding of prima facie obviousness***Rational and Motivation***

(MPEP 2142-2143)

Positional isomers, having the same radical on different positions of the molecule, are *prima facie* obvious, and require no secondary teaching. The experienced Ph.D. synthetic organic chemist, who would make Applicants' compounds, would be motivated to prepare these position isomers based on the expectation that such close analogues would have similar properties and upon the routine nature of such position isomer experimentation in the art of medicinal chemistry. It would be routine for the chemist to vary the point of attachment in order to increase potency and to establish better patent protection for her compounds. The teaching of U.S. 5,948,793 shows that the pyridazine moiety was already associated with the desired activity. In this case it would be obvious for these compounds to have the same activity at the acetylcholine receptors and indeed they do. *In re JONES* 74 USPQ 152 (4-methyl naphthyl-1-acetic acid and 2-methyl naphthyl-1-acetic acid obvious over a reference teaching 1-methyl naphthyl-2-acetic acid), quoted with approval by *Ex parte MOWRY AND SEYMOUR* 91 USPQ 219, *Ex parte Ullyot* 103 USPQ 185 (4-hydroxy-1-oxo-1,2,3,4-tetrahydroisoquinoline obvious over a reference teaching 4-hydroxy-2-oxo-1,2,3,4-tetrahydroquinoline), "[p]osition isomers are recognized by chemists as similar materials", *Ex parte BIEL* 124 USPQ 109 (N-ethyl-3-piperidyl diphenylacetate obvious over a reference teaching N-alkyl-4-piperidyl diphenylacetate), "[appellant's arguments] do not, in any way, obviate the plain fact that appellant's DACTIL is an isomer of McElvain et al.'s compound. This close relationship places a burden on appellant to show some unobvious or unexpected beneficial properties in his compound in order to establish patentability", *Ex parte Henkel* 130 USPQ 474, (1-phenyl-3-methyl-4-hydroxypyrazole obvious over reference teaching 3-phenyl-5-methyl-4-hydroxypyrazole), "appellants have made no comparative showing here establishing the distinguishing characteristics they allege which we might consider as evidence that the claimed compounds are unobvious. It is clear from *In re Henze*, supra, and the authorities it cites, that at least this much is necessary to establish patentability in adjacent homologs and **position isomers** (emphasis added)".

In re Surrey 138 USPQ 67, (2,6-dimethylphenyl-N-(3-dimethylaminopropyl) carbamate obvious over a reference teaching 2,4-dimethylphenyl N-(3-dimethylaminopropyl) carbamate), *In re MEHTA* 146 USPQ 284, (2-(1-methyl)-pyrrolidylmethyl benzilate obvious over a reference teaching 3-(1-methyl)-pyrrolidylmethyl benzilate), "[t]he fact that a **position isomer** (emphasis added) of a compound is known is some evidence of the obviousness of that compound.

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Position isomerism (emphasis added) is a fact of close *structural* (emphasis in original) similarity ...". *Deutsche Gold-Und Silber-Scheideanstalt Vormals Roessler v. Commissioner of Patents*, 148 USPQ 412, (1-azaphenothiazines obvious over references teaching 2-azaphenothiazines, 3-azaphenothiazines, and 4-azaphenothiazines), *In re Crounse*, 150 USPQ 554 (dye with *para* (CONH₂) and *ortho* (OCH₃) obvious over a dye with the same nucleus and *meta* (CONH₂) and *para* (OCH₃) group), *Ex parte Allais*, 152 USPQ 66, (3-β-aminopropyl-6-methoxyindole obvious over a reference teaching 3-β-aminopropyl-5-methoxyindole), *In re Wiechert* 152 USPQ 247, (1-methyl dihydrotestosterones obvious over a reference teaching 2-methyl dihydrotestosterones), *Monsanto Company v. Rohm and Haas Company*, 164 USPQ 556, at 559, (3',4'-dichloropropionanilide obvious over references teaching 2',4'-dichloropropionanilide and 2',5'-dichloropropionanilide), *Ex parte Naito and Nakagawa*, 168 USPQ 437, (3-phenyl-5-alkyl-isothiazole-4-carboxylic acid obvious over a reference teaching 5-phenyl-3-alkyl-isothiazole-4-carboxylic acid), "[t]his merely involves **position isomers** (emphasis added) and under the decisions cited, the examiner's holding of *prima facie* obviousness is warranted." *In re Fouche*, 169 USPQ 429, (10-aliphatic substituted derivatives of dibenzo[a,d]cycloheptadiene obvious over reference teaching 5-aliphatic substituted derivatives of dibenzo[a,d]cycloheptadiene). *In re Hass* 60 USPQ 552, which found a *prima facie* case of obviousness of 1-chloro-1-nitrobutane over 1-chloro-1-nitroisobutane taught in the prior art, *In re FINLEY*, 81 USPQ 383, 2-ethyl hexyl salicylate over octyl salicylate.

Ex parte Engelhardt, 208 USPQ 343 at 349, "[i]f functional groups capable of withdrawing or repelling electrons are located in the chain or **ring** (emphasis added) of a biologically active compound, transfer of such groups to other positions in which their electronic effects are lessened or enhanced may alter the biological activity of the modified compound. Hence, **position isomerism** (emphasis added) has been used as a tool to obtain new and useful drugs", *In re Grabiak* 226 USPQ 870, "[w]hen chemical compounds have "very close" structural similarities and similar utilities, without more a *prima facie* case may be made", *In re Deuel* 34 USPQ2d 1210, "a known compound may suggest its analogs or isomers, either geometric isomers (*cis v. trans*) or **position isomers** (emphasis added) (*e.g. ortho v. para*)".

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A reference is good not only for what it teaches by direct anticipation but also for what one of ordinary skill in the art might reasonably infer from the teachings. (*In re Opprecht* 12 USPQ 2d 1235, 1236 (Fed Cir. 1989); *In re Bode* 193 USPQ 12 (CCPA) 1976). In light of the forgoing discussion, the Examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a). From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

One of ordinary skill is also one of "ordinary creativity, not an automaton". See *Leapfrog Enterprises Inc. v. Fisher-Price. and Mattel Inc.* UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT "An obviousness determination is not the result of a rigid formula disassociated from the consideration of the facts of a case. Indeed, the common sense of those skilled in the art demonstrates why some combinations would have been obvious where others would not. See *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. , 2007 U.S. LEXIS 4745, 2007 WL 1237837, at 12 (2007) ("The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results.").

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned

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with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

5. Claims 37-40, 44-46, 56 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-7, 11-20, 29 of copending Application No. 10/591,871. Although the conflicting claims are not identical, they are not patentably distinct from each other because the Markush structures of the instant claims overlap with those of the '871 application. The instant species are also contained in the Markush of the '871 application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

5. Claims 37-40, 44-46, 56 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-11, 13-21, 23 of copending Application No. 11/663,152. Although the conflicting claims are not identical, they are not patentably distinct from each other because the Markush structures of the instant claims overlap with those of the '152 application. The instant species are also contained in the Markush of the '152 application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

6. No claims are allowed. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David K. O'Dell whose telephone

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number is (571) 272-9071. The examiner can normally be reached on Mon-Fri 7:30 A.M.-5:00 P.M EST.

7. If attempts to reach the examiner by telephone are unsuccessful, the examiner's Primary examiner, Rita Desai can be reached on (571)272-0684. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

D.K.O.

RITA DESAI
PRIMARY EXAMINER
RDesai
11/6/07